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Determinants of diagnostic performance of ^{18}F-FDG PET/CT in patients with fever of unknown origin

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Determinants of diagnostic performance of ^{18}F-FDG PET/CT in patients with fever of unknown origin

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Objectives **There is uncertainty about patient selection and the adequate timing at which fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET/computed tomography (CT) is indicated in the diagnostic work-up of fever of unknown origin (FUO). The aim of this study was to determine the diagnostic performance of ^{18}F-FDG PET/CT in patients with FUO.**

Methods **All consecutive patients who underwent ^{18}F-FDG PET/CT at the University Hospital Zurich because of FUO between 2006 and 2012 were included in this retrospective, observational study.**

Results **A total of 76 patients [70% men, median (interquartile range) age 60 (47–67) years] were included. ^{18}F-FDG PET/CT showed characteristically increased ^{18}F-FDG activity in 56 patients (74%), leading to confirmation of or change in the suspected cause of FUO in 57 and 17%, respectively. The final diagnosis after ^{18}F-FDG PET/CT included infection (21%), malignancy (22%), noninfectious inflammatory disease (12%), others (5%), or an unknown cause (40%). The success rate, sensitivity, and specificity of ^{18}F-FDG PET/CT were 60, 77, and 31%, respectively. Sensitivity was highest in patients with suspected malignancy (100%, 95% confidence interval 79–100%). Diagnostic performance was independent of the investigated variables other than suspected infection as a cause of FUO (odds ratio 0.1, 95% confidence interval 0.01–0.8, $P = 0.033$).**

Conclusion **The diagnostic performance of ^{18}F-FDG PET/CT was significantly higher in patients with suspected malignancy causing a FUO compared with suspected infection or noninfectious inflammatory disease. However, it was independent of the baseline characteristics and duration of fever. This supports the recommendation to perform ^{18}F-FDG PET/CT early in the diagnostic work-up of FUO, which may shorten disease duration and lower health costs, particularly when infection or malignancy is suspected.** ***Nucl Med Commun*** **37:57–65 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: ^{18}F-FDG activity, ^{18}F-FDG PET/CT, diagnosis, diagnostic performance, fever of unknown origin

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Background

Fever of unknown origin (FUO) was originally defined in 1961 by Petersdorf and Beeson [1] as an illness with recurrent fever of more than 38.3°C lasting 3 weeks or more, and without a diagnosis after 1 week of detailed clinical investigation. To satisfy modern outpatient-based medicine, Durack and Street [2] suggested shortening the duration of investigations to three inpatient days or three outpatient visits. However, as investigations in outpatient and inpatient settings are difficult to compare, different causes of FUO would be found. Instead of using arbitrary quantitative time criteria, a quantitative criterion of obligatory investigations was implemented in the definition [3]. Since then, FUO is defined as follows [4]: (a) temperature of at least 38.3°C on at least two occasions, (b) duration of illness of at least 3 weeks or multiple febrile episodes in at least 3 weeks, (c) not immunocompromised, (d) diagnosis uncertain despite thorough assessment of history, physical examination, and the following investigations: erythrocyte sedimentation rate or C-reactive protein, hemoglobin, platelet count, leukocyte count and differentiation, electrolytes, creatinine, total protein, protein electrophoresis, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, antinuclear antibodies, rheumatoid factor, microscopic urinalysis, ferritin, three blood cultures, urine culture, chest radiography, abdominal ultrasonography, and tuberculin skin test.

The cause of FUO is mainly classified into four categories including infection, malignancy, noninfectious inflammatory disease (NIID), and unknown cause [5–7]. Early identification and precise localization of the cause of FUO are crucial for the appropriate treatment of some distinct causes. However, despite advances in diagnostic techniques, it remains a clinical challenge to identify the etiology of FUO.

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PET using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is a well-established imaging tool for detection of malignancy [8–12]. Inflammatory cells and tumor cells share a similar molecular basis of ^{18}F-FDG uptake, for example overexpression of glucose transporter (GLUT-1 and GLUT-3) and glycolytic enzymes. Studies have indicated that ^{18}F-FDG PET is a valuable imaging technique for the diagnosis of infection and inflammation, and is a promising tool in the diagnostic work-up of FUO [5,13–16]. Although the first combined PET/computed tomography (CT) system became operational in 2001 already [17], only a small number of studies have assessed ^{18}F-FDG PET/CT in patients with FUO [18–27]. Furthermore, it is not clear when to perform an ^{18}F-FDG PET/CT for diagnostic work-up of FUO. The aim of the present study was to determine the diagnostic performance of ^{18}F-FDG PET/CT in patients who present themselves with FUO, and to define patient characteristics in which an ^{18}F-FDG PET/CT makes a significant contribution toward determining the cause.

Methods

Patients

All consecutive inpatients and outpatients who underwent ^{18}F-FDG PET/CT at the University Hospital Zurich because of FUO between 1 January 2006 and 30 June 2012 were included in this retrospective, observational study. Eligible patients were identified in the radiology information system using various subject headings including 'FUO', 'fever of known origin', 'unexplained fever', and 'fever of unknown cause or reason'. Thereafter, on the basis of the patient records, all adults were included who fulfilled a modified definition of FUO including (a) temperature of at least 38.3°C on at least two occasions and (b) duration of illness of at least 3 weeks or multiple febrile episodes in at least 3 weeks [1,4]. The patients were divided into four categories of FUO according to the publications of Durack and Street [2]: classical, nosocomial, HIV-associated, and immunodeficiency (neutropenia) as we did not exclude immunocompromised patients from the study.

Table 1 Patient and fever characteristics before ^{18}F-FDG PET/CT

Characteristic	Value
Male sex [*n* (%)]	53 (69.7)
Age (years) [median (IQR)]	60 (47–67)
Pre-existing medical conditions [*n* (%)]	
Malignancy	23 (30.3)
HIV	4 (5.2)
Solid organ transplantation	8 (10.5)
Travel to tropical regions within 6 months [*n* (%)]	5 (6.5)
Addiction to illicit drugs [*n* (%)]	7 (9.2)
Grouping of FUO [*n* (%)]	
Classical FUO	56 (73.3)
HIV-associated	4 (5.2)
Neutropenia	1 (0.8)
Symptoms [*n* (%)]	
Constitutional (night sweats, loss of weight)	19 (25.0)
Respiratory	25 (32.9)
Abdominal	27 (35.5)
Arthralgia	16 (21.1)
Myalgia	24 (31.6)
Cephalgia	12 (15.8)
No concurrent symptoms	16 (21.1)
Fever [*n* (%)]	
Continuous	20 (26.3)
Periodic or intermittent	56 (73.7)
Duration (days)	57 (30–182), range: 21–1460
Medication [*n* (%)]	
Corticosteroid	25 (32.9)
Immunosuppressant (other than corticosteroids)	12 (15.8)
Antibiotic	46 (60.5)
Chemotherapy	5 (6.6)
NSAID	13 (17.1)
Antipyretic	23 (30.3)

CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin; IQR, interquartile range.

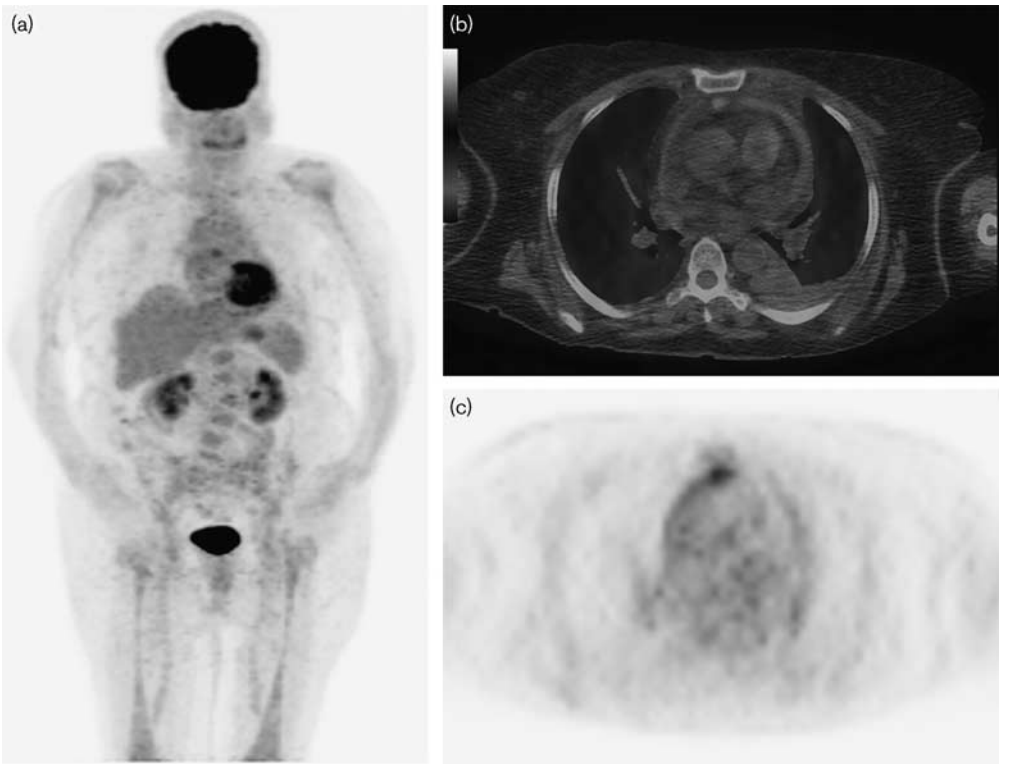
Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Canton of Zurich, Switzerland (KEK-ZH 2012–0308), and is registered at *http://www.clinicaltrials.gov* (Identifier: NCT01840891).

^{18}F-FDG PET/CT imaging

Patients fasted for at least 4 h and had no insulin injections 4 h before ^{18}F-FDG administration. Body weight, height, and blood glucose level were measured before injection of ^{18}F-FDG. In nondiabetic patients, blood glucose levels less than 8 mmol/l were accepted for imaging and in diabetic patients blood glucose levels less than 12 mmol/l were accepted for imaging. After an intravenous injection of body weight-adapted ^{18}F-FDG (^{18}F-FDG dosage of 5 MBq/kg body weight), patients rested for a standardized uptake time of 60 min.

Data were acquired with the patient in the supine position with the arms overhead. Low-dose CT for attenuation correction was acquired from the mid-thigh to the vertex of the skull with the following scan parameters: tube voltage, 140 kVp; tube current time product, 10–80 mAs/slice; pitch of 1.4; collimation, 64 × 0.625 mm; rotation time, 0.5 ms; and field of view 50 cm. Directly after CT data acquisition, PET data were acquired using the 3D mode with a fixed scan duration of 2 min per bed position and a field of view of 157 mm. Emission data were corrected for randoms, dead time, scatter, and attenuation. CT data for attenuation correction and anatomical referencing were reconstructed with a slice thickness of 3.75 mm and an increment of 3.0 mm using a filtered back reconstruction algorithm. Attenuation-corrected axial PET images were reconstructed using a standard iterative ordered subset expectation maximization 3D algorithm (matrix size, 256 × 256, Fourier rebinning, 3D ordered subset expectation maximization with eight iterations, 16 subsets). Scans were performed using an integrated PET/CT system (Discovery VCT; GE Healthcare, Milwaukee, Wisconsin, USA).

Fig. 1



Results from a 73-year-old patient presenting with fever. PET/CT provided a diagnosis of pericarditis that responded immediately to antibiotic treatment. (a) Maximum intensity projection 60 min after an injection of 352 MBq ^{18}F-FDG. (b) Axial slice of fused PET/CT images, showing metabolically active pericarditis. (c) Axial slice of the corresponding PET image. CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose.

Interpretation and analysis of ^{18}F-FDG PET/CT

The nuclear physician reading the ^{18}F-FDG PET/CT at the Department of Nuclear Medicine had knowledge of the patient's clinical history and results of previous imaging studies. Any ^{18}F-FDG uptake was considered pathologic or positive when intensity was higher than that in surrounding tissues and it was not localized in an area with a physiologic biodistribution of the radiopharmaceutical. A negative ^{18}F-FDG PET/CT finding was present when tracer activity was only detectable in areas of physiologic uptake of ^{18}F-FDG and when no sites of increased uptake were visible. In line with previous studies [3,22–24], the diagnostic performance was defined as follows: a true positive finding was considered when ^{18}F-FDG PET/CT showed a pathological tracer uptake as the cause of FUO, which was confirmed by further investigations (biopsy) or clinical follow-up. A pathological ^{18}F-FDG uptake, which was not confirmed as the cause of FUO, was considered false positive. A negative ^{18}F-FDG PET/CT finding was considered true negative when no cause of FUO was found despite extensive diagnostic work-up and a follow-up of 3 months. It was considered false negative when there was evidence of an infection, NIID, or malignancy as a cause of FUO despite a normal ^{18}F-FDG PET/CT finding. Furthermore, the success rate of ^{18}F-FDG PET/CT was defined as 'helpful' or 'noncontributory' according to their effect on the determination of the final diagnosis (cause of FUO).

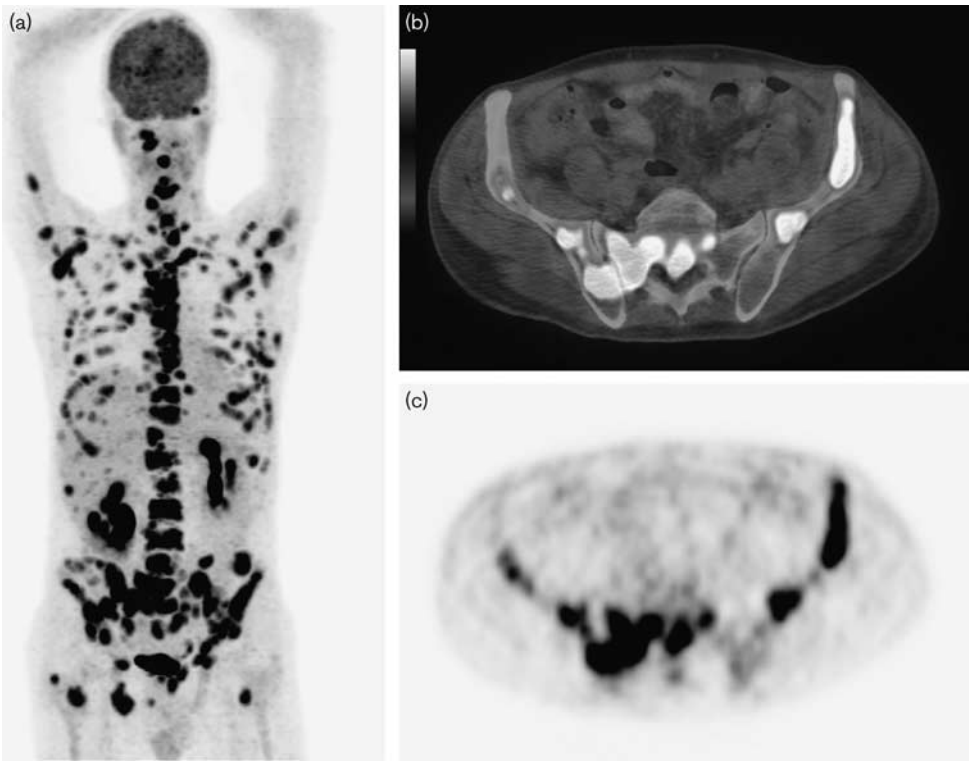
Outcome measures

The primary outcome was to determine the success rate and diagnostic performance of ^{18}F-FDG PET/CT in patients presenting with FUO. The secondary outcome was to investigate possible determinants of a helpful ^{18}F-FDG PET/CT considering various variables [sex, age, duration, and characteristics of the fever (intermittent vs. continuous FUO), constitutional symptoms, inflammatory markers, FUO classification according to Durack and Street [2], and suspected cause of FUO]. The suspected and final diagnoses had been made by study-independent, treating physicians. According to this, the diagnoses were classified into the following groups: infection, NIID, malignancy, or indefinite/unknown as proposed elsewhere [5–7].

Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 22 (IBM Corporation, Armonk, New York, USA). Continuous data are reported

Fig. 2



Results from a 42-year-old patient presenting with fever. PET/CT showed Hodgkin's disease with bone marrow manifestation only. (a) Maximum intensity projection 60 min after an injection of 327 MBq ^{18}F-FDG. (b) Axial slice of fused PET/CT images, showing multiple metabolically active bone marrow manifestations. (c) Axial slice of the corresponding PET image. CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose.

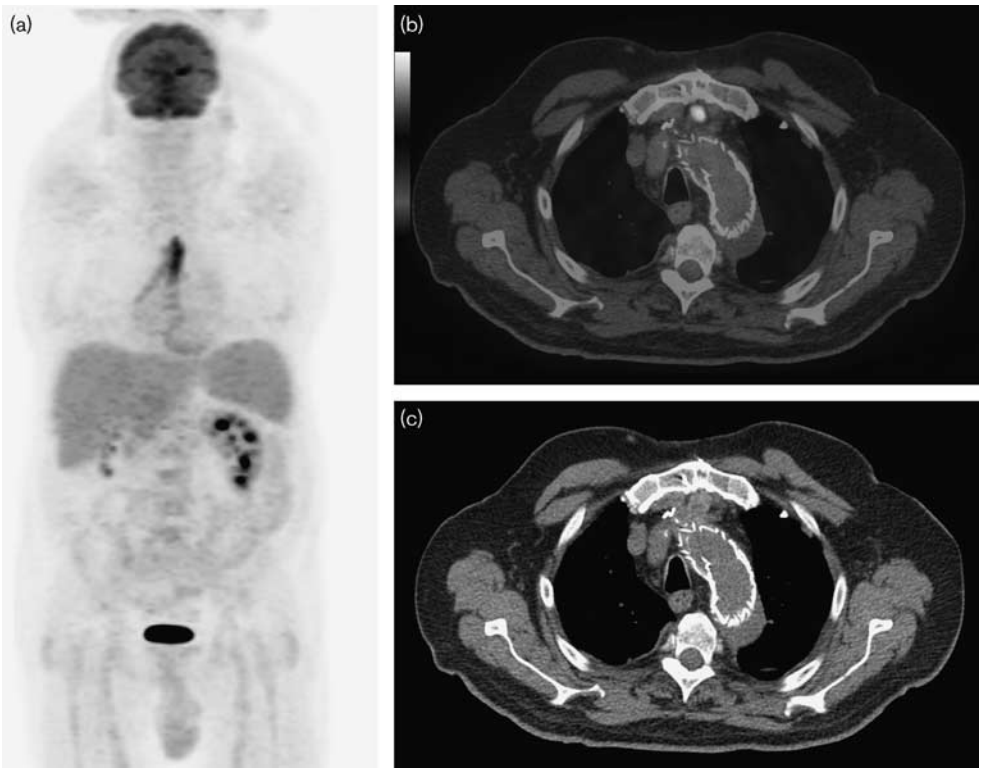
as median [interquartile range (IQR)] and categorical data are reported in absolute counts (percentages). Helpful and noncontributory ^{18}F-FDG PET/CT findings were compared using the χ^2-test (categorical variables) or Student's *t*-test (continuous variables). A univariable logistic regression model was first used to assess the individual effect of each covariate on the success rate of ^{18}F-FDG PET/CT. Variables with a *P*-value equal to or less than 0.1 in the univariable analysis were entered into the multivariable regression analysis. *P*-values of all outcomes were two-sided; a value less than 0.05 was considered to indicate statistical significance. For sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio, the 95% confidence intervals were calculated.

Results

Of 176 patients who were identified using one of the search terms, 100 had to be excluded because of various reasons: definition of FUO not fulfilled ($n=82$), no follow-up data ($n=8$), missing informed consent ($n=8$), and incomplete data ($n=2$). A total of 76 patients [69.7% men, median age 60 (47–67) years] were included in this study (Table 1 and Figs 1–4). Pre-existing risk factors for FUO were present in 46.1% (malignancy, HIV infection, or solid organ transplantation). The majority of patients were classified as having 'classical FUO,' 73.7%. The most prevalent concurrent symptom was gastrointestinal discomfort (pain or nausea) in 35.5%. In 21.1%, fever was the only symptom. The fever was intermittent or periodic in 73.7% of patients, whereas only 26.3% had continuous fever. Its median (IQR) duration before ^{18}F-FDG PET/CT was 57 (30–182) days, with a median (IQR) maximum body temperature of 39.1 (38.8–40.0)°C. Laboratory investigations before ^{18}F-FDG PET/CT are listed in Table 2. The median values of inflammation parameters were moderately elevated, and patients were anemic, whereas median leukocytes and procalcitonin values were within normal ranges. In most patients, a CT of the chest ($n=54$, 71%) and/or the abdomen ($n=57$, 75%) had been carried out before the ^{18}F-FDG PET/CT, without conclusive results. Echocardiography to rule out endocarditis had been performed in 45 patients (42%). On the basis of the examinations performed before ^{18}F-FDG PET/CT, the suspected cause of FUO was infection ($n=37$), malignancy ($n=22$), NIID ($n=12$), or unknown ($n=5$).

^{18}F-FDG PET/CT indicated pathological ^{18}F-FDG activity in 56 patients (73.7%), leading to confirmation of

Fig. 3

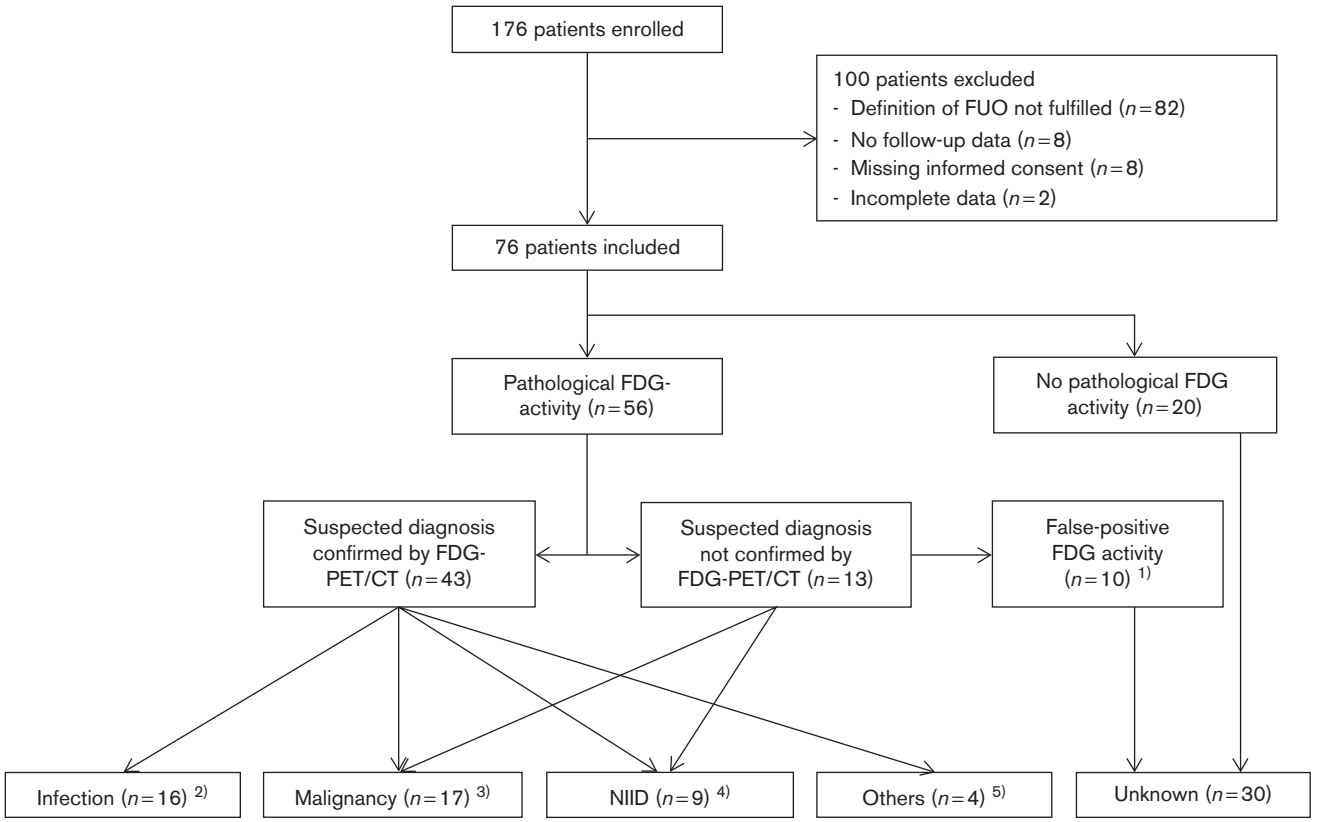


Results from a 68-year-old patient presenting with intermittent fever 4 years after aortic graft replacement. PET/CT showed vascular graft infection. (a) Maximum intensity projection 60 min after an injection of 386 MBq ^{18}F-FDG. (b) Axial slice of fused PET/CT images showing metabolically active foci adjacent to the graft. (c) Axial slice of the corresponding CT image, showing discrete fluid collection retrosternally. CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose.

the suspected cause of FUO in 56.6% (43/76) of the cases (Fig. 4). In 17.1% (13/76), there was an ^{18}F-FDG PET/CT finding, which was incongruent with the suspected cause and led to an alternative diagnosis (Fig. 4). In three of these patients, the final diagnosis was Hodgkin lymphoma ($n=2$) and pericarditis ($n=1$), and in 10 patients, there were false-positive ^{18}F-FDG uptakes. In 20/76 patients (26.3%), there was no pathological ^{18}F-FDG activity. These negative ^{18}F-FDG PET/CT findings were more prevalent in patients with an unknown suspected cause of FUO before ^{18}F-FDG PET/CT (4/5, 80.0%) compared with suspected infection (11/37, 29.7%), malignancy (1/22, 4.5%), or NIID (5/12, 41.7%) ($P=0.004$). The final diagnosis after ^{18}F-FDG PET/CT was infection ($n=16$), malignancy ($n=17$), NIID ($n=9$), other ($n=4$), and unknown cause ($n=30$). Almost 50% ($n=14$) of the patients with an unknown final diagnosis achieved spontaneous resolution of the fever within 3 months. Confirmation of the suspected cause after ^{18}F-FDG PET/CT was possible in 59.1 und 58.3% of patients with suspected malignancy and NIID, respectively. In contrast, confirmation was only possible in 32.4% of patients with suspected infection. Also, the rate of unknown causes of FUO was highest among patients with suspected infection (48.6%) and in those with an unknown suspected cause (80.0%). As a whole, the proportion of patients with an unknown final diagnosis increased significantly after ^{18}F-FDG PET/CT ($P<0.001$, Table 3).

The diagnostic performance of ^{18}F-FDG PET/CT in patients presenting with FUO irrespective of fever quality, classified according to fever quality and the suspected cause of FUO, is presented in Table 4. The sensitivity of ^{18}F-FDG PET/CT was higher in patients with intermittent FUO compared with those with continuous FUO, and in patients with suspected malignancy compared with those with suspected infection or NIID. However, these differences did not reach statistical significance ($P=0.079$ and 0.082, respectively). Specificity was low irrespective of the subgroup. In 46/76 patients (60.5%), ^{18}F-FDG PET/CT was considered useful in finding the cause of FUO. Patient characteristics classified according to the success rate of ^{18}F-FDG PET/CT are shown in Table 5. The success rate of ^{18}F-FDG PET/CT was significantly higher in patients with constitutional symptoms ($P=0.015$) and with suspected malignancy ($P=0.039$). The duration and quality (intermittent vs. continuous) of fever was comparable between helpful and noncontributory ^{18}F-FDG PET/CT findings.

Fig. 4



Study flow chart. [1]Chronic anemia ($n=5$), hemorrhoids ($n=2$), recent trauma ($n=2$), or ankylosing spondylitis ($n=1$). [2]Pulmonary infection ($n=4$), lymphadenitis ($n=3$), pericarditis ($n=2$), tuberculosis of the bone marrow ($n=2$), colitis ($n=1$), mycotic aortic aneurysm ($n=1$), liver abscess ($n=1$), inguinal abscess ($n=1$), vascular graft infection ($n=1$). [3]Lymphoma ($n=13$), gastric cancer ($n=1$), lung cancer ($n=1$), colon cancer ($n=1$), thyroid cancer ($n=1$). [4]Vasculitis ($n=3$), polymyalgia rheumatica ($n=2$), sacroileitis ($n=1$), sarcoidosis ($n=1$), lupus erythematosus ($n=1$), rheumatoid arthritis ($n=1$). [5]Hemophagocytic syndrome ($n=2$), drug fever ($n=1$), common variable immune deficiency syndrome ($n=1$). CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin.

Table 2 Laboratory values before ^{18}F-FDG PET/CT

BSR (mm/h) [mean (SD)]	66.4 (38.9)
C-reactive protein (mg/l) [median (IQR)]	83 (22–155)
Procalcitonin (ng/ml) [median (IQR)]	0.2 (0.1–1.0)
Hemoglobin (g/l) [median (IQR)]	109 (89–124)
Leukocytes ($\times10^3$/µl) [median (IQR)]	7.2 (4.6–11.3)
Neutrophils ($\times10^3$/µl) [median (IQR)]	4.3 (2.3–8.0)
Thrombocytes ($\times10^3$/µl) [median (IQR)]	286 (173–443)
Ferritin (µg/l) [median (IQR)]	526 (213–896)

BSR, blood sedimentation rate; CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; IQR, interquartile range.

However, the success rate of ^{18}F-FDG PET/CT with intermittent FUO was 64% compared with 50% in patients with continuous fever. Determinants with a possible effect on the success rate of ^{18}F-FDG PET/CT in terms of the cause of FUO are shown in Table 6. In the multivariable analysis, suspected infection was associated negatively with the success rate of ^{18}F-FDG PET/CT (odds ratio 0.1, 95% confidence interval 0.01–08, $P=0.033$).

Discussion

^{18}F-FDG PET/CT is a valuable imaging technique for the diagnosis of infection and inflammation. Therefore, its use has increased markedly in the last few years for the diagnostic work-up of FUO [5,13–16]. However, there is uncertainty in terms of the adequate timing at which an ^{18}F-FDG PET/CT is indicated in the diagnostic work-up of FUO. The aim of this retrospective study was to determine the clinical usefulness of ^{18}F-FDG PET/CT for FUO and to define determinants of its diagnostic performance. However, most of the studies investigating ^{18}F-FDG PET/CT in patients with FUO are difficult to compare because of the heterogeneity of the patient population, differences in ^{18}F-FDG PET/CT techniques, and the stages at which it was performed.

The reported success rate and sensitivity of ^{18}F-FDG PET/CT in patients with FUO ranges between 33 and 75% and 72 and 100%, respectively [14,19,20,23–27]. This is in line with our own findings of a success rate of 61% and a sensitivity of 77%. The final diagnosis

Table 3 Rates of changed causes of FUO on the basis of ^{18}F-FDG PET/CT

	After ^{18}F-FDG PET/CT				
	Confirmed infection	Confirmed NIID	Confirmed malignancy	Confirmed other diagnosis[a]	Unknown cause of FUO
Before ^{18}F-FDG PET/CT					
Suspected infection ($n=37$)	12 (32.4)	1 (2.7)	3 (8.1)	3 (8.1)	18 (48.6)
Suspected NIID ($n=12$)	1 (8.3)	7 (58.3)	0	1 (8.3)	3 (25.0)
Suspected malignancy ($n=22$)	3 (13.6)	1 (4.5)	13 (59.1)	0	5 (22.7)
No suspected cause of FUO ($n=5$)	0	0	1 (20.0)	0	4 (80.0)

Data are presented as *n* (%).
CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin; NIID, noninfectious, inflammatory disease.
[a]Other diagnoses included central thermoregulation disorder ($n=2$) and adverse effect of a drug ($n=2$).

Table 4 Diagnostic performance of ^{18}F-FDG PET/CT in patients with FUO irrespective of fever quality classified according to fever quality (intermittent vs. continuous) and according to the suspected cause of FUO

	Sensitivity	Specificity	NPV	PPV	LR+	LR−
All patients ($n=76$)	77.3 (62.2–88.5)	31.3 (16.1–50.0)	50.0 (27.2–72.8)	60.7 (46.8–73.5)	1.12 (0.9–1.5)	0.73 (0.3–1.5)
Intermittent FUO ($n=56$)	83.3 (67.2–93.6)	30.0 (11.9–54.3)	50.0 (21.1–78.9)	68.2 (52.4–81.4)	1.19 (0.86–1.64	0.56 (0.21–1.50
Continuous FUO ($n=20$)	50.0 (15.7–84.3)	33.3 (9.9–65.1)	50.0 (15.7–84.3)	33.3 (9.9–65.1)	0.75 (0.34–1.67)	1.50 (0.52–4.32)
Suspected infection ($n=37$)	72.2 (46.5–90.3)	31.6 (12.6–56.6)	54.5 (23.4–83.2)	50.0 (29.9–70.1)	1.06 (0.69–1.60)	0.88 (0.32–2.38)
Suspected NIID ($n=12$)	57.1 (18.4–90.1)	40.0 (5.3–85.3)	40.0 (5.3–85.3)	57.1 (18.4–90.1)	0.95 (0.36–2.49)	1.07 (0.27–4.23)
Suspected malignancy ($n=22$)	100 (79.4–100)	16.7 (0.42–64.1)	100 (2.5–100)	76.2 (52.8–91.8)	1.20 (0.84–1.72)	0.00

Values are presented in % (95% CI).
CI, confidence interval; CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin; LR, likelihood ratio; NIID, noninfectious, inflammatory disease; NPV, negative predictive value; PPV, positive predictive value.

Table 5 Patient characteristics classified according to the success rate[a] of ^{18}F-FDG PET/CT in patients with FUO

Patient characteristics	^{18}F-FDG PET/CT helpful[a] ($n=46$)	^{18}F-FDG PET/CT noncontributory[a] ($n=30$)	*P*-value
Age (years)	56.5 (15.1)	56.4 (14.6)	0.98
Male sex [*n* (%)]	29 (63.0)	24 (80.0)	0.12
Duration of fever (days)	134.1 (176.3)	187.6 (337.2)	0.37
Continuous FUO [*n* (%)]	10 (21.7)	10 (33.3)	0.26
Constitutional symptoms [*n* (%)]	16 (34.8)	3 (10.0)	0.015
Classical FUO[b] [*n* (%)]	29 (63.0)	27 (90.0)	0.026
C-reactive protein (mg/l)	91.6 (79.1)	112.3 (93.9)	0.31
Leukocytes ($\times 10^6$/l)	7.6 (4.7)	9.3 (6.4)	0.20
Previous antibiotic treatment [*n* (%)]	22 (56.4)	24 (64.9)	0.49
Previous immunosuppressive treatment [*n* (%)]	12 (30.8)	13 (35.1)	0.81
Suspected cause of FUO [*n* (%)]			0.039
Infection	19 (41.3)	18 (60.0)	
NIID	9 (16.6)	3 (10.0)	
Malignancy	17 (37.0)	5 (16.7)	
Unknown	1 (2.2)	4 (13.3)	

Continuous data are presented as mean (± SD) and categorical data are presented as *n* (%).
CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin; NIID, noninfectious, inflammatory disease.
[a]The success rate of ^{18}F-FDG PET/CT was classified in 'helpful' or 'noncontributory' findings according to their effect on the determination of the final diagnosis (cause of FUO).
[b]Classification of FUO according to Durack and Street [2].

remained unclear in 39% of the FUO patients despite performing an ^{18}F-FDG PET/CT, which is within the average range of other publications of between 34 and 46% [14,15,28]. Furthermore, in 17% of the cases, ^{18}F-FDG PET/CT detected a cause of FUO, which had not been suspected on the basis of preceding reasoning and examinations including abdominal and chest CT. Similarly, Federici *et al.* [18] singled out ^{18}F-FDG PET/CT as the only successful diagnostic tool in 23% of patients with FUO. However, the overall diagnostic performance of ^{18}F-FDG PET/CT was very modest (negative predictive value 50%, positive predictive value 61%).

Our comparatively large study adds to previous knowledge as we found that the success rate of ^{18}F-FDG PET/CT was associated negatively in patients with suspected infection, but also in patients with suspected NIID causing FUO. Perhaps, the negative impact of a suspected infection or NIID on the success rate is because of a missing focal pathological uptake of ^{18}F-FDG in some kind of infections or NIID (such as endocarditis lenta, familial Mediterranean fever, or Still's disease). Furthermore, this could be one reason for the difference in reported data on sensitivity as the final diagnoses in several studies were heterogeneous. For example, malignancy was the cause of FUO, with an incidence

Table 6 Logistic regression analysis of possible determinants of a helpful ^{18}F-FDG PET/CT in patients with FUO

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.0 (0.9–1.1)	0.98		
Sex (male)	0.4 (0.1–1.1)	0.12		
Duration of fever	1.0 (0.9–1.1)	0.37		
Continuous FUO[a]	0.6 (0.2–1.6)	0.26	0.5 (0.2–1.6)	0.28
Classical FUO[b]	0.0.3 (0.06–1.0)	0.13		
CRP	0.9 (0.9–1.0)	0.30		
Leukocytes	0.9 (0.8–1.0)	0.21		
Previous antibiotic treatment	1.4 (0.6–3.6)	0.45		
Previous immunosuppressive treatment	1.2 (0.5–3.2)	0.69		
Suspected cause of FUO[a]				
Infection	0.1 (0.01–0.8)	0.034	0.1 (0.01–0.8)	0.033
NIID	0.3 (0.1–1.0)	0.054	0.3 (0.1–1.1)	0.068
Malignancy	0.8 (0.2–4.6)	0.88	0.9 (0.2–5.1)	0.97

CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; ^{18}F-FDG, fluorine-18 fluorodeoxyglucose; FUO, fever of unknown origin; NIID, noninfectious, inflammatory disease; OR, odds ratio.
[a]Included in multivariable analysis.
[b]Classification of FUO according to Durack and Street [2].

ranging between 3 and 20% [23,25]. In the present study, 22% of the cases were attributed to neoplasia.

The success rate of ^{18}F-FDG PET/CT in the present study was independent of variables such as age and sex, as well as periodicity and duration of the fever, and inflammatory parameters. The influence of the duration of fever on the success rate is an inconsistent finding of three earlier studies [14,26,28]. Whereas the diagnostic performance of ^{18}F-FDG PET/CT was not associated with the duration of FUO in the prospective studies of Bleeker-Rovers *et al.* [14] and Buysschaert *et al.* [28], there was a significant improvement in the success rate of ^{18}F-FDG PET/CT in patients, with a mean of 19 compared with 30 days of fever in the study of Gafter-Gvili *et al.* [26]. According to others [4,20,27], we support the recommendation of performing PET/CT early in the diagnostic work-up of FUO, albeit the duration of fever does not seem to influence its diagnostic performance. However, the optimal timing to perform ^{18}F-FDG PET/CT in patients with FUO remains to be investigated in a future study. Presumably, the optimal timing range may be the third week after the onset of fever, suggesting that ^{18}F-FDG PET/CT may substitute CT of the chest and abdomen. According to a recently proposed algorithm, ^{18}F-FDG PET/CT should be performed after obligatory baseline examinations including laboratory tests, chest radiography, and abdominal ultrasonography, but before chest and abdomen CT, which may be futile after ^{18}F-FDG PET/CT [4]. In our study, ^{18}F-FDG PET/CT was performed despite a previous CT scan of the chest or the abdomen in 60% of the cases. However, early ^{18}F-FDG PET/CT may shorten the period of diagnostics and disease as well as save cost in the amount of 5471 euros per patient [29] as it may avoid the need for further futile investigations [14,15]. In our institution, the costs of a whole-body ^{18}F-FDG PET/CT are approximately twice as high as the cost of a contrast-enhanced CT of the thorax and abdomen. Moreover, early identification of patients with malignancy may improve their outcome. As almost 50% of the patients with an unknown cause of FUO after ^{18}F-FDG PET/CT achieved spontaneous resolution of the fever, a wait-and-see period may be indicated in these patients if the clinical situation is stable.

Limitations

There are several limitations to the present results, which are primarily because of the retrospective study design, that is PET/CT scans were read by one of our experienced nuclear medicine physicians (all at least with 5 years of experience in nuclear medicine in a high-volume center with more than 5000 PET/CT examinations per year); readers were not blinded to clinical information as the examinations were part of the clinical work-up of the patients, thus reflecting the 'real-life-situation'. Second, there was no set time point at which to perform an ^{18}F-FDG PET/CT for FUO. Thus, it was performed on the basis of the clinician's decision. This may have introduced selection bias and further heterogeneity. Third, ^{18}F-FDG PET/CT imaging was only performed from the mid-thigh to the vertex of the skull; therefore, infectious foci in the legs may have been missed. Fourth, it is difficult to reliably determine the diagnostic performance in patients with FUO as the confirmation of the final diagnosis as the gold standard is not well defined and, again, heterogeneous between different studies. Fifth, compared with others, specificity was low in our series, which may be because of the heterogeneity of our study population.

Conclusion

The success rate and sensitivity of ^{18}F-FDG PET/CT in patients with FUO were 61 and 77%, respectively. The success rate was associated negatively in patients with suspected infection. However, the success rate was independent of the duration of fever, which supports the recommendation of performing ^{18}F-FDG PET/CT early in the diagnostic work-up of FUO to shorten disease duration and lower health costs, particularly when malignancy is suspected. However, one must keep in mind that the cause of FUO after ^{18}F-FDG PET/CT remains unclear in 40% of the cases. In these patients, a wait-and-see period may be justified. Prospective studies investigating the precise timing and predictors of ^{18}F-FDG PET/CT in patients with FUO need to be designed.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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